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SYSTEMATIC REVIEW ON APPLICATION OF NANOTECHNOLOGY IN WOUND HEALING AND ULCER

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ABSTRACT

Wound healing and ulcer is a complex process and has been subjected of any intense research for a longtime. Its management have more socio economic impact on clinical practices. Most skin lesion are called wound and primarily are divided into chronic and acute. Ulcer presently called as chronic wound. Nanotechnology is the study of extremely small structure having size of 0.1 to100nm.Nanomedicineis relatively new yield of science and technology. Biomaterials arises through nanotechnology have dramatically expanded the range of tools used for injection control and accelerate wound healing. Nano materials that including polymeric metallic and ceramic based nanomaterial that could used as therapeutic delivery agent to accelerate regeneration of damaged dermal and epidermal tissue. Nano engineered biomaterials have tremendously improve the range of tools utilized for control of as well as acceleration of healing of diabetic foot ulcer, Over the few decades potential nonomaterial like polymeric and metallic nanoparticle and electro spasm nanofibers for DFU treatment. Nanoparticle incopraed hydro gel or amoxicillin for eradiation of H.pylori. This review based on the different methods and type of nanoparticle in the most recent development in wound healing and ulcer diagnosis including silver oxide nanoparticle alleviated indomethacin, nanoparticle incorporated hydrogel, tripolyphosphate nanoparticle. Apart from this reviw focused on the nanoparticle enhance effect of stimulate cell proliferation and shorter the wound healing time.

KEYWORD: Gene therapy, growth factor, nbacterial infection, biomaterial, hyaluronic acid, inflammation process, wound healing, ulcer, silver, gold, nanoparticle, nanotechnology.

1. INTRODUCTION

'Small is beautiful'-this should the slogan of nonscientist. The nanotechnology has arises from engineering and molecular biology and are leading to the development of the structures, device and systems in the atomic molecular and macromolecular size range bearing a capacity to revolutionize medical, therapeutic and diagnosis which has never unmet earlier.[1] The Nobelist Richard Feynman first predicted the future emergence of new science in 1959, which deals with the structure on a scale of 1-100nm. Fifty years after the unpredictable result in ability to manipulate material on the scale which is used by nature while currently nanoscale reaches the µm level.

Nanoparticle has new and improved property when compared to the large particle of the bulk. New property due to change in the size, distribution and the morphology of particle. Nanomedicine involves the cutting-edge combination of nanotechnology with medicin. Nanodevice is having wide range of advantages that is it can enter into the cytoplasmic space across the cellular barrier like Trojan horses, activation of specific transport mechanism and improve their bioavailability, biocompatibility and the safety profiles.[2] Nanoparticle have a wide range of application in combating microbes, biolabeling, and in the treatment of cancer. Nanoparticles used against different pathogenic strains, especially green synthesized nanopoticle. Photochemical nanoparticles are found an important tool for antimicrobial drug delivery. Nanoparticleshas amazing advantages in the treatment of wound healing and ulcer. Wound healing are classically defined as a series of continues or overlapping events. That is phases of hemostasis, inflammation, granulation and remodeling.[3] The cytokines and growth factors are secreted at the site of wound by inflammatory cells and other stromal cell in response to injury are derived this events. Vascular endothelial growth factor(VEGT) and basic fibroblast growth factor(BFGF) are the major growth factor having the key role in the wound healing.[4]

Infection is the major problems for burn injuries as it delay the normal process of wound healing by prolonging the inflammatory phase of the immune response. Silver sulfadiazine(SSD) has been the standard optical antimicrobial for burn wounds. But it has some adverse effects such as argyria, leucopenia, hepatic and the renal toxicity. Therefore nanometer sized silverparticles are available which have surface to volume ratio and remain effective even at very low concentration and reduce the silver toxicity and also more effective against anti microbial organism which are used recently.[5]

Diabetic ulcer is the one of major complication and major site of ulceration is found in feet. It is sever because of persistent pain and chance of bacterial infection. Nnotechnology has been applied in electronic storage system biotechnology. Gold nanoparticcle are suspension of nanometer-sized particle of substances. Colloidal AUNPS have been prepared biomedical application due to unique surface, electronic and optical property.

Copper is essential elements increase may wound healing. Venous and diabetic ulcer are among most of 10 occurring chronic wound affecting million of the world due to the low copper level. Copper oxide is the nanosolution form of copper, which slowly release copper ion with the presence of moisture.[6]

GNP was formed due to chloroauric acid treated with T.terrestris fruit extrac. GNPS shared size dependent GNPs functionalized with chitosan and liposome are highly stable in gastric acid and capable of fusing with bacteria at pathological PH, making them suitable to treat gastric pathogen such as H pylori infections. It also have the catalectic activity for reduction of toxic, p-nitroaniline to p-phenilindiamine and other non toxic byproduct. Gastric pathogen such as H pylori infections. It also have the catalectic activity for reduction of toxic, p-nitroaniline to p-phenilindiamine and other non toxic byproduct.

In this review we highlight the most recent developed nanotechnology based therapeutic agent, viability, and efficiency of each treatment, on chronic cutaneus wound. Here explain the unmet need and future directions of current technology, and the strategies that can advances the wound healing field.

2. WOUND HEALING PROCESS

Wound healing process is classically defined as a sever of events which include heamostasis, inflammation, proliferation, epithelisation, maturation and remodeling.[7] (fig.1).

Heamostatic events occure immediately after injury. The body's innate response to vascular injury is a dynamic process that involve both physical and dynamic interaction to promote platelet aggregration and formation of blood clot. It is a quick response to control bleeding by minimizing unwanted thrombosis.[8]

This process take place by 3 steps

1) Platelet plug formation
2) Activation of coagulation cascade
3) Removal of cot through fibrolysis

The inflammatory phase beging immediately after injury and may continue up to 6 days. Inflamation is the first event that spontane-boldly begins immediately after injury. It is charatrisedby clotting and components of extracellular matrix(ECM. Activated monocyte aid in host defense.[9]

Proliferation phase begin between 4-21 days during the wounding. This phase characterized by formation of ECM and beginning of angiogenesis. Fibroblast and endothelial cells are primary cell involved in proliferation phase FGF and PDGF are stimulated the fibroblast to invade wound site andproduce collagen, elastase like ECM component to generate granulation of chemotaxis of inflammatory cells that help to cleanse the wound, Inflamation begins 1-4 days after wounding it involved the migration of receptor Into wounding site and followed by the macrophages, after that lymphocytes. once chemotaxis is completed, Inflammato, activated by local mediators, which release enzyme such as elatase, neutral protiense and colagense which proteolitocaly removedtha damaged tissue. Fibroblast secrete FGF aling with VEGF secreted by platelet and neutrophil act as angiogenic factor.this promote vasculization of at the site of wound healing by the stimulation of endothelial cell proliferation and migration. Fibroblast and endothelial cell are mastely invade thae wound site from karatinocyte at margin of wound which undergo a transient burst of proliferation which leads to epithelisation over wound.[10]

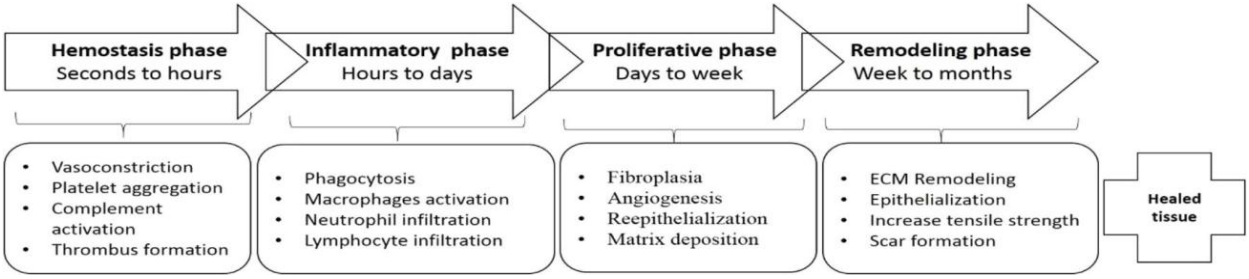

Fig. 1: Main biological phases in wound healing.

After 3 week of injury maturation phase begins and take up to 2 years to complete. The last step of normal wound healing is remodeling. Remodeling of ECM involve the balance between collagen synthesis and degranulation which operate by several enzymes such as matrix metalloprotease(MMPs), nuutrophil released elastase and gelatinase, colagenasees and stromelysis.[11]

3. GASTROINTESTINAL ULCERS

Bacterial infections are also the cause of wounds that do not heal in the mucosal environment, leading to gastrointestinal ulcers. Helicobacter pylori is the leading cause of gastrointestinal infection in adults and children worldwide. The treatment of H. pylori infection[12] is obstructed by two main factors:

1. Bacteria live beneath the gastric mucous lining attached to the gastric epithelium and, therefore, access to antimicrobial drugs to the site of infection is restricted
2. Antibiotics are not administered to the site of infection in effective concentrations and in fully active forms.

4. NANOPARTICLE FOR WOUND HEALING

The current nanoscale, both carrier and drug released that target the three phases of wound repair will be discussed, highlight the cellular events involved.

4.1. Nanoparticals-bearing endogenase molecule

The progration of healing phase was governed by the soluble active proteine throght modulation of cellular and molecular componend.[13] Bioactive proteins have gained progressive interest for progressive treatment of chronic dehiscent wound do to the control exerted on wound healing. The application of exogeniuse rcombinent growth factor to chronic wound involved in clinical trials have been contucted for the past 10 years in an attempt to find a way to accalerat wound healing. Although, the result of several trails are encouraging and but the over all result are discouraging. Only a single recombinant growth factor –recombinent humen PDGF-BB-has been approved by the united Food and Drug A administration and use only for diabetic foot ulcer.[14] Recently, the new possibilitie to enhance the biological efficacy of molecules through a controlled release for extended periods of time are opened by development of nanoscale system for drug delivery.[15] The end ogenous active molecule that have been engineered, nowadays included thrombin, nitric oxide, growth factor and opioids.

4.1.1. Thrombin

One of the first products of the hemostatic response is thrombin. It is essential for the conversion of fibrinogen to fibrin and is responsible for the aggregation of blood platelets in the formation of the "platelet plug", as well as for the activation of other hemostatic factors.[16] In human plasma, the half-life of thrombin is shorter than 15 s due to strict control by protease inhibitors and vessel wall components. To provide drugs with long-term protection of their natural inhibitors, enzymatic degradation and other adverse elements, it has been suggested that therapeutic drugs be conjugated with nanoparticles. In the Ziv-Polat laboratory[17], thrombin was conjugated with maghemite nanoparticles (iron oxide nanoparticles) for the treatment of incisional wounds in the skin of rats. The results obtained by analyzing the tensile strength and histological findings associated with the mechanical properties of the wound 28 days after treatment indicated that thrombin-conjugated nanoparticles accelerated the incisional wound healing significantly better than free thrombin and untreated wounds.

4.1.2. Nitric Oxide Release Nanoparticles

Recent studies have investigated the antimicrobial properties of nitric oxide (NO), a reactive free radical produced by inflammatory cells (eg, neutrophils and macrophages) during bacterial infection.[18] Using small molecules like NO donors, DeRosa et al. demonstrated that NO has a broad spectrum of antibacterial properties against Gram-positive and Gram-negative bacteria.Miller et al. reported the effectiveness of NO in the destruction of MRSA biofilms, which are complex communities that form when a group of microorganisms self-secretes a polysaccharide matrix that retains nutrients for constituent cells and protects them from the immune response and antimicrobial agents.[19] Barraud et al. reported that the small molecules they release do NOT promote cell dispersion in the biofilms of P. aeruginosa.[20] As an alternative strategy to administer NO to pathogenic bacteria, Hetrik et al. reported on the antibacterial properties of NO-releasing silica nanoparticles[63] that exhibited greater bactericidal efficacy against planktonic P. aeruginosa cells compared to small-molecule NO donors. The authors demonstrated that with respect to wounds, NO had beneficial side effects on the healing process by modulating inflammation, angigenesis and tissue remodeling. As it is known that wounds are deficient in NO[21], the application of NO-releasing silica nanoparticles can accelerate healing by killing bacteria and overcoming the general NO deficiency.

4.1.3. Growth factors

Growth factors have the potential to accelerate the healing process by attracting cells to the wound site (TGF-β), promoting cell migration, stimulating proliferation of epithelial cells and fibroblasts (FGF and PDGF), as well as initiating formation of new blood vessels (FGF and VEGF), and finally participating in the remodeling of the scar.[22] One way to improve the in vivo efficacy of growth factors, avoiding degradation of proteolytic enzymes, is to stabilize protein structure and biological activity, prolonging the time on which growth factors are released at the delivery site. The period of release of the drug from a polymer matrix can be regulated by the load of the drug, the type of polymer used and the processing conditions. Delivery systems have been designed in a variety of configurations and have been manufactured from different types of natural

and synthetic polymers, both degradable and non-degradable. Poly (lacticacide) (PLA) and poly (lactic-co-glycolic acid) (PLGA) has proven to be suitable biocompatible and biodegradable materials. To achieve long-term in vivo circulation, the surface is generally modified with polyethylene glycol (PEG), reducing elimination by the rticuloendothelial system. Particle delivery systems explored the gelatin microparticles embedded in TGF-β, EGF in PLA microspheres, FGF in gelatin microspheres and PLGA nanospheres embedded in PDGF.[23] The particles show some limits that are associated with the use of organic solvents in the production process, which leads to contamination and toxicity of the product. Therefore, alternative manufacturing techniques have been proposed, such as spray drying, which is based on the use of supercritical fluids (especially CO2) and offers the advantages of mentally safe and cheap beingen viron. Zavan et al. They offered a notable recent application of this technology for the delivery of growth factors in vivo: Hyaluronan-based porous nanoparticles (HYAFF11) with PDGF were incorporated as a system designed for the in vivo treatment of skin ulcers. PDGF has been known since 1986 for successfully promoting the healing of chronic wounds through the stimulation of chemotaxis, proliferation and deposition of ECM. HYAFF11, the benzyl ester of hyaluronic acid, is a biopolymer that has found numerous applications for in vitro reconstruction of the skin, as well as for the in vivo regeneration of smaller teries and veins. HYAFF particles have the ability to absorb growth factors and to release them in a temporally and spatially event-driven manner. This timed and localized release of PDGF promoted optimal tissue repair and which regeneration of full thickness wounds.

4.1.4. Opioids

Recently Wolf et al.[24] indicated that opioids improve wound healing by promoting keratinocyte migration. This new finding is of great interest because one of the side effects of a severe skin wound is severe pain. For an effective reduction of pain, the topical application of opioids seems advantageous. Bigliardi and others[25] first developed nanoparticle carriers to increase the penetration of opioids into the skin and delay the release of the loaded drug. Experiments in the HaCaT human keratinocyte-derived cell line showed that opioids stimulated cell migration and closure of experimental wounds. Increased migration depended on concentration and could be blocked by naloxone, an opioid receptor antagonist, indicating a specific opioid receptor interaction. model. In standardized wounds, the keratinocytes almost completely covered the equivalent of the dermis after 4 days, which That was not the case when applying the discharged particles. In conclusion, acceleration of wound closure, low cytotoxicity and irritation, as well as the possible prolonged release of morphine make solid lipid nanoparticles an interesting approach to innovative wound management.

4.2. Antibiotics with nanoparticles

With respect to antibiotics, the most effective treatments for H. pylori infection are combinations of two antibiotics (for example, clarithromycin, tetracycline or metronidazole) and a proton pump inhibitor. At present, therapeutic approaches are available in standard tablet formulations; Therefore, the drug is released in the stomach and provides a localized effect. In fact, therapy options are preferably selective and locally active with limited availability for other tissues.[26]

Ramteke et al. have prepared gliadin nanoparticles containing clarithromycin and omeprazole with desolvation methods using pluronic F-68 as a stabilizing agent.[27] Gliadin is defines a group of polymorphic proteins extracted from gluten that are soluble in an ethanolic solution and which show a remarkably low solubility in water, except at extreme pH. Due to these physicochemical properties, gliadin nanoparticles can be prepared by desolvation methods for macromolecules using environmentally acceptable solvents like as ethanol and water. These macromolecules showed high drug loading capacity and were soluble without further chemical or physical crosslinking. The fluorescent polystyrene nanoparticles were studied by Hasani et al.[79] in a detailed analysis of adhesion to ulcerated gastric tissue. After induction of gastric ulcers in mice, nanoparticle therapy was administered and inflammation was monitored by myeloperoxidase activity, a reliable index that quantifies the infiltration of activated neutrophils into inflamed tissue.[29] At the end of the treatment, the confocal laser scanning microscopy analyzes qualitatively located the particles and the fluorescent spectroscopy quantitatively determined the deposition of particles. The results confirmed that nanoparticle deposition was significantly higher in ulcerated tissues compared to healthy tissues and that embedded drug nanoparticles acted in selected areas.[30]

4.2.1. Heparin

A complete study of pH-sensitive chitosan / heparin nanoparticles for stomach-specific anti-H. Pylori therapy was performed by Lin et al.[31] The nanoparticles are appeared to have a particle size of 130–300 nm, with a positive surface charge and were stable at a pH of 1.2–2.5 and which allowed them to protect the incorporated amoxicillin from destructive gastric acids. Through in vivo studies, they demonstrated that the prepared nanoparticles adhered and infiltrated the cell-cell junctions and interacted locally with H. pylori infection sites in intercellular spaces.

4.3. Silver-based nanoparticles

The use of silver for the treatment of ulcers has been reported since the 5th century BC. C. In the seventeenth and eighteenth centuries, silver nitrate was already used for the treatment of ulcers. The antimicrobial activity of silver was indroduced in the 19th century. However, after the introduction of antibiotics in 1940, the use of silver salts decreased. Subsequently, silver salts and

silver compounds have been used in different biomedical fields, especially in the treatment of burns.[32] The antimicrobial activity of silver seems high: due to its multi-level antibacterial effects (including resistance to multiple drugs) and low systemic toxicity, it provides an antibacterial effect that greatly reduces the chances of developing resistance. Nanotechnology has provided the means to produce pure biostable silver nanoparticles, either through photo-assistance reduction and ionic stabilization or loading of the metallic particles in nanofibers. In all cases, 7–20 nm silver nanoparticles exhibited antibacterial (especially anti-Gram negative) and antifungal activity, and are also synergistic to common antibiotic therapy (streptomycin, kanamycin and polymyxinB). In vivo studies also demonstrated a direct promotion of wound healing by silver nanoparticles through the reduction of cytokine-modulated inflammation: silver-induced neutrophil apoptosis, decreased MMP activity and a negative modulation in TGF- β resulted in a total acceleration of the wound healing rate and reduction of hypertrophic scars.[33]

Although the progressive expansion of the therapeutic application of silver nanoparticles, the use of a metal compound leads to possible side effects that must be taken into account. Studies have been investigating the biosecurity of silver as a therapeutic agent, reporting an acceptable biocompatibility, although the occasional development of argyria (a bluish-gray cosmetic color of the skin).

4.4. Nanoparticles and gene therapy

Polymeric gene delivery systems offer several advantages for the delivery of plasmid DNA, such as protection against nuclease degradation and controlled prolonged release. The potential retained by the modulation of gene expression in the wound healing process led researchers to request a system designed for DNA transfection. In reality, transfection capacity has been tested in vitro: biocompatible and biodegradable PLGA polymers were designed to obtain high plasmid loading efficiency and then were loaded with an antiangiogenic plasmid DNA (pFlt23k). PLGA nanoparticles were prepared with a supercritical fluid emulsion extraction based on CO2: this allowed a high pDNA load (19.7%, w / w), high loading efficiency (> 98%) and low residual solvents (<50ppm). VEGF secretion by epithelial cells was significantly reduced, showing a potential value in the treatment of wound disorders in which VEGF is elevated. Masotti and Ortaggi recently described a nanofabrication method that can be useful for obtaining small chitosan nanospheres that contain DNA (38 ± 4 nm) for biomedical applications.[34] Its method based on informed osmosis has general applicability to various synthetic or natural biopolymers, resulting in nanostructured systems of different size and shape that can be used in various applications Biotechnology Chellat et al. They also recently took advantage of the biochemical properties of chitosan to analyze nanoparticles loaded with DNA in a human macrophage cell line to study the possible modulation of the expression of proinflammatory cytokines, metalloproteinases and their specific inhibitors.[11] However, zymography studies showed that secreted MMPs were in their proactive form, while in the presence of nanoparticles containing 10 and 20 μg / ml DNA, the active form of MMP-9 was detected, but not MMP-2, in cell lysates. The results obtained were significant only for a greater secretion of metalloproteinases, possibly related to phagocytosis of nanoparticles.

4.5. Nanoparticles and Stem Cells

Stem cells have great potential as cell-based therapies to promote vascularization, hair follicle reconstruction and tissue regeneration. Yang et al. they have developed transiently modified stem cells that express highly VEGF for the purpose of promoting angiogenesis.[35] Non-viral biodegradable polymeric nanoparticles were developed to deliver the hVEGF gene to human mesenchymal stem cells and cells derived from human embryonic stem cells. The treated stem cells demonstrated a markedly improved hVEGF production, cell viability and graft in target tissues. Implantation of scaffolds seeded with VEGF-expressing stem cells (hMSCs and hESdCs) led to a vessel density two to four times greater 2 weeks after implantation, compared to control cells or cells transfected with VEGF through Lipofectamine 2000, a leading commercial reagent. A total of 4 weeks after intramuscular injection in the mouse ischemic hind limbs, genetically modified human mesenchymal stem cells substantially improved angiogenesis and limb recovery while reducing muscle degeneration and tissue fibrosis. These results indicate that stem cells manipulated with biodegradable polymer nanoparticles can be therapeutic tools to vascularize tissue constructs and treat ischemic disease.[36]

4.6. Gold nanoparticles

Gold nanoparticles (AuNP) are biocompatible and are widely used in tissue regeneration, targeted drug administration and wound healing. Unlike silver, gold nanomaterials as a single material alone do not offer any antimicrobial activity. Therefore, AuNPs must be incorporated with other biomolecules to be used effectively in biomedical applications. When AuNPs cross-link with collagen, it can easily integrate with other biomolecules such as polysaccharides, growth factors, peptides and cell adhesion molecules, joining the gold surface without changing the structure of the collagen. These modified AuNPs demonstrate properties such as biocompatibility and biodegradability and, therefore, can be widely used in wound healing. Like collagen, gelatin and chitosan can also be easily associated with AuNP, which shows Safe and positive effects to improve wound healing.

Gold could be conjugated with existing antimicrobial drugs or with other nanoparticles, increasing their

potential to eliminate microbes microbes. fold and showed significant activity against E. coli, a gram-negative bacterium that is generally unaffected by vancomycin.[37] Gold nanomaterials can also be conjugated with pathogen-specific antibodies for photothermal therapy, or with photosensitizing molecules for photodynamic therapy (PDT) to achieve antimicrobial activity. For example, Sherwani et al. showed that a photosensitizer conjugated with AuNP showed greater antifun1gal activity against wounds infected by CANDIDAALBICANOS in mice. In a recent study, the topical application of AuNPs applied to skin wounds in rats showed better healing property due to increased reepithelialization, granulation tissue formation and increased ECM deposition and collagen content.[38] These differences, especially found in the first healing periods, reduce the total duration of healing. When monotherapy with AgNP and monotherapy with AuNP was compared in an in vitro wound healing study using rats, subsequent therapy showed increased free radical removal activity and improved wound healing.[38]

4.7. Zincoxide Nanoparticles

Zincoxide (ZnO) is an inorganic antibacterial agent. Which is more stable than organic agents. Zinc, which has a life time in living cells, is a chemical element and is essential for wound healing, especially wound healing and burns. It has been reported that topical application of zinc reduces inflammation, improves epithelialization and reduces bacterial growth in chronic wounds. Zinc, being the cofactor of metalloproteinase, also plays a vital role in the generation of ECM. ZnO nanoparticles possess antibacterial, anti-inflammatory and antiseptic properties, and are widely used in the production of cosmetics and creams for skin and ointments. The wound healing effect of ZnO nanoparticles is based on the concentration and size of the nanoparticles. ZnO has more antibacterial activity due to its small size and high surface-volume ratio. When ZnO is embedded with a chitosan hydrogel, it exhibits a strong antibacterial activity, which makes it an appropriate component in wound dressing materials. ZnO nanoformulation, using it as a biocompatible polymer, can improve efficacy at lower doses. In addition, zinc also acts as a regulator for keratinocyte migration and auto-fa autocytosis, which are critical for normal wound repair. ZnO follows a biphasic process which releases Zn ions from the nanomaterial. Initially, when Zn ions meet with biological fluids, it undergoes rapid hydration to form hydrated ZnO, which acts as a bactericidal agent.

4.8. Nanoengineering scaffolds for wound healing

A significant aspect of the current therapeutic agents used in wound healing involves the engineering of nanopolymeric scales to mimic the properties of the ECM, that is, their fibrous nature and their nanoscale characteristics. Sevaral nanotechnology techniques are used for the formation of scales, including electro-spinning, self-assembly and phase parathion. Among these methods, electro-spinning is the main choice for the manufacture of nano fibers. The electro-spinning is a well established technique for the engineering of porous fibrous nano fibers, which has been successfully tested in the generation of nanoscabras that demonstrate properties Physical and structural analogous to those of ECM. Electrospin nano fibers derived from a combination of PLGA / SF silk fibrin were used as hybrid scales to promote fibroblast binding and proliferation to improve healing of diabetic wounds

4.9. Copper nanoparticles

Copper plays a key role in angiogenesis and in the synthesis and stabilization of extracellular matrix skin proteins and which are critical processes of skin formation. We presume that the introduction of copper into wound dressings would improve wound repair. The application of wound dressings containing copper oxide to infected wounds in genetically modified diabetic mice resulted in an increase in the gene and up-regulation in situ of proangiogenic factors (e.g., Placental growth factor, hypoxia-1 alpha inducible factor and vascular endothelial growth factor), increased blood vessel formation ($p < 0.05$) and increased wound closure ($p < 0.01$) compared to control dressings (without copper) or commercial dressings for wounds containing silver. This study demonstrates the ability of wound dressings containing copper oxide to improve wound healing and sheds light on the molecular mechanisms by which dressings impregnated with copper oxide stimulate wound healing.

CONCLUSION

The treatment of chronic wound healing and ulcer are difficult challenge because current therapies are failed to provide and complete process of wound healing is critical for general wellbeing of any patient.

Nanotechnology offers great opportunity in impairing wound healing treatment. We need to enhance the knowledge about the nanotechnology and nanomedicine. It's magical benefict in curing of stomach ulcer will be a milestone as compared to traditional treatment. We need to be a carefull about the risk while handling nanoparticle. However they have difficult to gathering enough information about the physiological property of nanoscale and theire anticipated behavior and toxicity in human body. They have many advantages given by the size (I,e.., they can easily pass through the skin barrier), some unpredictable events could occur as well as. For example, nanoparticles may interfere with some functions of protiene on the surface of cell. Or be taken up into cells and bind to intracellular molecules. The binding of polymers and liposomes with phyto-fabricated nanoparticles could exhibit as a potential against H,pylori and will treat an ulcer with huge efficacy**.**

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